



James Hunter
President
Validus Pharmaceuticals, LLC
119 Cherry Hill Road, Suite 310
Parsippany, NJ 07054

RE: NDA 011961
Marplan (isocarboxazid) tablets
MA# 21

Dear Mr. Hunter,

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a healthcare professional webpage (MAR-018-12)¹ for Marplan[®] (isocarboxazid) tablets (Marplan) submitted by Validus Pharmaceuticals, LLC (Validus) under cover of Form FDA-2253. The webpage is false or misleading because it omits and minimizes important risk information associated with Marplan, overstates the efficacy, and presents unsubstantiated claims regarding the drug. The webpage, therefore, misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a), (n) & 321(n). See 21 CFR 202.1(e)(5)(i)(iii); (e)(6)(i) (e)(7)(i).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Marplan.²

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) (in pertinent part):

Marplan is indicated for the treatment of depression. Because of its potentially serious side effects, Marplan is not an antidepressant of first choice in the treatment of newly diagnosed depressed patients.

...

The antidepressant effectiveness of Marplan in hospitalized depressed patients, or in endogenomorphically retarded and delusionally depressed patients, has not been adequately studied.

The effectiveness of Marplan in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to

¹ Last accessed on May 6, 2013 (<http://www.marplan.com/professionals/clinical-trials>)

² This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

use Marplan for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

The PI for Marplan includes a Boxed Warning regarding suicidality and antidepressant drugs. The contraindications for Marplan include the following drug or food combinations: other monoamine oxidase inhibitors (MAOIs or MAO-Is) or dibenzazepine-related entities; bupropion; selective serotonin reuptake inhibitors (SSRIs); buspirone; sympathomimetics (including amphetamines) or over-the-counter drugs that contain vasoconstrictors; meperidine; dextromethorphan; cheese or other foods with a high tyramine content; anesthetic agents; some central nervous system depressants (including narcotics and alcohol); antihypertensives; thiazide diuretics; antihistaminic drugs; and excessive quantities of caffeine. Marplan is also contraindicated in the following patient populations: patients with confirmed or suspected cerebrovascular defect or any patient with cardiovascular disease, hypertension, or a history of headache; patients with pheochromocytoma, patients with a history of liver disease or in those with abnormal liver function tests; and patients with severe impairment of renal function.

The PI also contains the following warnings: screening patients for bipolar disorder; second line status; hypertensive crises; possibility of hypotension, faintness, and drowsiness sufficient to impair performance of potentially hazardous tasks; and limited experience with Marplan at higher doses. The PRECAUTIONS section of the PI includes recommendations regarding pediatric use, hypotension, lower seizure threshold, and hepatotoxicity.

The most commonly observed adverse reactions in adult patients treated with Marplan ($\geq 5\%$ and at least twice the incidence in placebo patients) were nausea, dry mouth, and dizziness.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The webpage presents numerous efficacy and safety claims regarding Marplan, but omits important material risks associated with the drug. For example, while the webpage includes the claim, “**MAO-inhibitors are contraindicated with certain drugs**” (emphasis original), it fails to disclose the specific drugs and/or drug classes that should not be used in combination with Marplan. As stated in the PI, Marplan is contraindicated in combination with other MAOIs or dibenzazepine-related entities; bupropion; SSRIs; buspirone; sympathomimetics or over-the-counter drugs that contain vasoconstrictors; meperidine; dextromethorphan; anesthetic agents; some central nervous system depressants; antihypertensives; thiazide diuretics; antihistaminic drugs; and excessive quantities of caffeine. This omission of material risk information is particularly concerning because the concomitant use of Marplan with several of these contraindicated drugs, including SSRIs and merperidine, can cause serious, and sometimes fatal, adverse reactions.

Additionally, the webpage fails to disclose that Marplan is contraindicated in combination with cheese or other foods with high tyramine content. While we acknowledge that the webpage

includes the following information, “[p]otential hypertensive crises may occur with foods that contain tyramine” (emphasis original), it fails to communicate the fact that foods with high tyramine content are contraindicated in combination with Marplan. Furthermore, the aforementioned information regarding hypertensive crises omits important material facts regarding this serious and potentially fatal risk. Specifically, the webpage fails to disclose that hypertensive crises associated with Marplan treatment can be fatal and result from the “**coadministration of MAOIs and certain drugs and foods**” (bold emphasis original, underlined emphasis added). The webpage also fails to disclose that blood pressure should be monitored closely in patients treated with Marplan, and that treatment should be discontinued immediately if palpitations, frequent headaches, or hypertensive crisis occurs.

The webpage also omits the following patient populations in which Marplan is contraindicated: patients with confirmed or suspected cerebrovascular defect or any patient with cardiovascular disease, hypertension, or a history of headache; patients with pheochromocytoma, patients with a history of liver disease or in those with abnormal liver function tests; and patients with severe impairment of renal function.

The webpage also omits risk information from the WARNINGS TO PHYSICIANS section of the PI regarding Screening Patients for Bipolar Disorder, Second Line Status, Warnings to Patients, and Limited Experience with Marplan at Higher Doses. Additionally, the webpage omits risk information from the PRECAUTIONS and ADVERSE REACTIONS sections of the PI. OPDP acknowledges the statement, “**Please see Full Prescribing Information including BOXED WARNINGS . . .**” (emphasis original), located at the bottom of the webpage; however, it does not mitigate the omission of this important risk information from the webpage.

By omitting serious and, in some cases, potentially fatal risks associated with Marplan, the webpage misleadingly suggests that Marplan is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Minimization of Risk

Promotional materials are misleading if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of information related to the effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. Specifically, the webpage prominently presents the efficacy information at the top of the page, using colorful graphics, and large bolded headers. In contrast, the limited risk information is relegated to the very bottom of the webpage, below the product logo, tagline, footnotes, and link to the references cited in the webpage. This presentation misleadingly minimizes the risks of Marplan because the risk information does not appear as an integral part of the webpage, unlike the claims and presentations regarding the efficacy. As the product logo, tagline, footnotes, and link to references often signal the end of the piece, the viewer may assume that the information placed below are unimportant and unrelated to the main message.

In addition, the webpage does not present any significant signal to alert the viewer that important risk information follows the presentation of benefit information. We note the statement **“Please see Important Safety Information, Including Boxed Warning, Below”** (emphasis original), at the very top of the webpage, above the product logo, link to the “Patients and Caregivers” website, and tabs for other webpages within the healthcare provider site. This statement, however, is inadequate to mitigate this misleading risk presentation.

Therefore, the overall effect of this presentation undermines the communication of important risk information, minimizes the risks associated with Marplan, and misleadingly suggests that Marplan is safer than has been demonstrated.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The webpage presents claims such as the following:

- “Using the ‘intent-to-treat’ sample method, authors concluded that Marplan[®] (isocarboxazid) Tablets exhibited a 41.3% average difference vs. placebo.”
- “‘Intent to treat’ samples in 5 of these 12 studies revealed a Marplan[®] (isocarboxazid) Tablets efficacy rate of 60.1%”
- “In 8 of these 12 studies, the ‘Adequate Treatment’ sample method showed a Marplan[®] (isocarboxazid) Tablets efficacy rate of 68.2% among patients receiving at least a minimum number of weeks of treatment.”

These claims overstate the efficacy of Marplan in the treatment of depression. Specifically, these claims present efficacy rates of 41.3% to 68.2% in patients treated with Marplan, when these efficacy rates are not supported by substantial evidence or substantial clinical experience. The reference³ cited to support these claims is a publication which describes a literature review and meta-analyses examining the efficacy of several MAOIs, including isocarboxazid (Marplan). The meta-analyses for isocarboxazid were based on a literature review and may have produced a biased sample of studies since failed or negative clinical trials are not often published in the medical literature. Furthermore, the clinical studies used to conduct the meta-analyses for isocarboxazid were performed in diverse patient populations, with different doses of the drug, and under varying clinical conditions. Thus, the cited reference does not constitute substantial evidence or substantial clinical experience to support these or any other similar claims.

³ Thase ME et al. MAOIs in the Contemporary Treatment of Depression. *Neuropsychopharm.* 1995; 12(3):185-219.

In addition, the webpage includes the following claims:

- “In one of 7 placebo-controlled studies in the meta-analysis, Giller et al (1984) as cited in Thase, 16 out-patients who were crossed over from placebo (due to lack of response) achieved a 69% rate with Marplan® (isocarboxazid) Tablets treatment.”
- “At the close of this 2-stage trial, 18% of patients on placebo and 92% of Marplan (isocarboxazid) Tablets-treated patients had improved (11 of 12 patients who were fair to poor responders to tricyclics). Recalculating this results on a base of the full 16 patients originally crossed over, the improvement on Marplan® (isocarboxazid) Tablets as 69% as cited in the Thase et al meta-analysis.”
- “Data for the 24 patients who completed the full 6-weeks (3-week placebo phase and 3-week open phase) of the study showed that 92% of the Marplan® (isocarboxazid) patients improved vs. 18% of the patients on placebo.”

The reference⁴ cited in support of the above claims describes a two-phase clinical study. Phase one was a double-blind, placebo-controlled clinical study, whereas phase two was an open-label clinical study, enrolling placebo-treated patients from phase one who still met symptom criteria for depression. This study, however, does not constitute substantial evidence or substantial clinical experience to support these claims. Specifically, a portion of the data described in the efficacy claims above was collected during the open-label, phase two portion of the clinical study. However, results from an open-label clinical study with no control group do not constitute substantial evidence or substantial clinical experience to support this, or any other, efficacy claims. Only efficacy data obtained from well-designed and adequately controlled studies may be used to support efficacy claims.

Furthermore, the claim “[a]uthors observed a significant clinical improvement in the Marplan® (isocarboxazid) Tablets-treated patients (56%) vs. patients given placebo (18%)” references data from the above study³ regarding the Clinical Global Assessment (CGA) scale. Data from a global measure (i.e. the CGA) alone are not sufficient to support efficacy claims for Marplan.

The webpage also includes the following presentation (emphasis original):

In the **Giller, Bialos, Riddle and Waldo study**⁵, a 1988 24-week multi-axial open-label outcome assessment of Marplan® (isocarboxazid) Tablets’ effectiveness in 43 adult outpatients with major depressive disorder, 4 outcome areas were evaluated: symptoms, work, family functioning, and social functioning.

...

Results:

- After 6 weeks on Marplan® (isocarboxazid) Tablets therapy, the “symptoms” outcome area improved the most.

⁴Giller, E, et al. Assessing Treatment Response to the Monoamine Oxidase Inhibitor Isocarboxazid. *J Clin Psychiatry*. 1984; 45:44-48.

⁵ Giller E et al. MAOI treatment response: multi-axial assessment. *J Affective Disorders*. 1988; 14:171-175.

- Among patients who completed the full 24 weeks of the study, all four outcome areas improved beyond their 6-week levels, and “study completers” who began to improve at week 6 continued to improve through week 24.
- Improvement in “work functioning” reached statistical significance among study completers ($p=0.0001$).
- In contrast to the early-on improvement in “symptoms”, the bulk of improvement in work functioning occurred between weeks 5 and 24 (not during the first 6 weeks) prompting the authors to comment that the need to continue Marplan[®] (isocarboxazid) Tablets therapy beyond initial symptom improvement “cannot be underestimated”.

The webpage cites an open-label, non-placebo-controlled clinical study⁴ in support of these claims. However, as indicated above, data derived from these types of studies (i.e. open-label with no control arm) do not constitute substantial evidence or substantial clinical experience to support claims of efficacy for Marplan.

Unsubstantiated Mechanism of Action Claims

The webpage contains the following claims and graphic presentation regarding the mechanism of action for Marplan (footnote omitted):

- “MAO inhibitors regulate the monoamine content of the central nervous system, but, unlike other types of antidepressants, MAO inhibitors raise the levels of all three of the neurotransmitters in the brain responsible for mood elevation (norepinephrine, serotonin, and dopamine).”
- Graphic presentation of the mechanism of action of Marplan in conjunction with the descriptions, “[a]rtists conception of neurotransmitters in the brain” and “[a]rtist’s conception of Marplan raising the levels of all three key neurotransmitters that elevate mood.”

These claims and graphic presentation misleadingly suggest a greater degree of certainty about the mechanism of action of Marplan than is currently known. As stated in the CLINICAL PHARMACOLOGY section of the PI (emphasis added):

Isocarboxazid is a non-selective hydrazine monoamine oxidase (MAO) inhibitor. . . . The mechanism by which MAO inhibitors act as antidepressants is not fully understood, but it is thought to involve the elevation of brain levels of biogenic amines. However, MAO is a complex enzyme system, widely distributed throughout the body, and drugs that inhibit MAO in the laboratory are associated with a number of clinical effects. Thus, it is unknown whether MAO inhibition per se, other pharmacologic actions, or an interaction of both is responsible for the antidepressant effects observed.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Marplan in violation of the FD&C Act, 21 U.S.C. 352(a), (n) & 321(n). See 21 CFR 202.1(e)(5)(i)(iii); (e)(6)(i); (e)(7)(i).

OPDP requests that Validus immediately cease the dissemination of violative promotional materials for Marplan such as those described above. Please submit a written response to this letter on or before May 20, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Marplan that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA# 21 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Marplan comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Jessica N. Cleck Derenick, PhD
Team Leader (Acting)
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, PharmD
Team Leader (Acting)
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA N CLECK-DERENICK
05/06/2013

MATHILDA K FIENKENG
05/06/2013